II. REMARKS

Preliminary Remarks:

Amendment of the specification

The specification is amended by correcting various clerical errors.

In response to paragraph no. 3 of the official action, the specification is also amended by correcting incorrect SEQ ID NOs and by inserting new SEQ ID NOs, where appropriate, pursuant to 37 C.F.R. 1.821(d).

In response to paragraph no. 5 of the official action which requires that the specification be amended to identify the date of the deposit of hybridoma 24-31 and the address of the depository, the applicants direct the examiner's attention to page 2 of the amendment that was filed on September 30, 2004, which added a paragraph to the specification with the requested information. A copy of the deposit receipt from the depository was also attached to the response that was filed on September 30, 2004.

The paragraph on page 33, beginning at line 27, is amended to correct errors in the description of the P and E modifications, and to update the reference to a co-assigned U.S. patent application. This paragraph erroneously describes the P and E modifications as respectively referring to the change of a leucine to a glutamic acid at position 236 and the change of a serine to a proline (Kabat numbering) at position 229. At the time the application was filed, one of skill in the art would have known that the "P" modification had previously been described by Angal et al. (Molecular Immunology, 1993, 30(1):105-108, copy attached) as the replacement of serine with proline (P) in the hinge region sequence -Cys-Pro-Ser-Cys-Pro- of a gamma 4 constant region (see Table 1, p. 105), and that the "E" modification had previously been described by Duncan et al. (Nature, 1988, 332(7):563-564, copy attached) as the replacement of leucine with glutamate (E) in the constant region hinge region sequence -Leu-Gly-Gly-Pro- (see p. 563, right column). One of skill in the art would therefore have recognized that the description of the P modification on page 33, lines 27-32, of the application is actually that of the E modification and vice versa - the description of the E modification in the application is actually that of the P modification.

In addition, the positions in the gamma 4 constant region polypeptide that are identified as being modified by the application (*i.e.*, positions 229 and 236) are the actual amino acid positions of the mutations with respect to amino acid no. 1 of the constant chain polypeptide, not the Kabat positions as indicated on lines 29-30 of page 33. This would also have been recognized by persons of skill in the art at the time of filing, as the amino acid sequence of a human gamma 4 constant region was known at the time the application was filed. For example, see the sequence described in Genbank accession no. P01861 (originally entered in SWISS-PROT; copy attached). From the amino acid sequence of the humanized heavy chain variable region disclosed in the application (*e.g.*, in Figure 6) and the published sequence of the gamma 4 constant region, it would have been clear to one of ordinary skill in the art at the time of filing that the positions of the P and E modifications identified in the application are not the Kabat positions, but are the actual amino acid positions of the mutations with respect to amino acid no. 1 of the constant chain polypeptide.

The reference to "Attorney Docket No. 012712-165 filed on September 6, 1995" on line s 30-31 of page 33 is amended to refer to "U.S. Patent Application No. 08/523,894, filed on September 6, 1995, which issued as U.S. Patent No. 6,136,310 on October 24, 2000". The text of U.S. Patent No. 6,136,310, incorporated by reference in its entirety into the present application, accurately describes the P and E modifications, and discloses a full-length heavy chain polypeptide from which it is clear that positions 229 and 236 refer to actual positions, and not Kabat positions (see columns 9 and 14, and Figures 4, 6, and 17, copies attached). The foregoing amendments of the paragraph that begins on line 27 of page 33 do not include new matter.

Amendment of the claims

Claims 2, 18, 30, 32, 33, and 34 are amended. Claims 2, 3, 5, 16-28, 30, and 32-38 are currently pending.

Independent claim 2 is amended to be directed to a method that comprises the step of assaying *in vitro* to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells selected from the group consisting of T-cell proliferation, the production of IL-2, the production of Il-4, and the production of IFN-γ. Support for the amendment is found on pages 35-36 of the application.

Amended claims 30, 32, 33, and 34 and new claims 39 specify that the human T-cell activation response of the claimed invention is an activation response by purified human $CD4^+$ T cells and is assayed *in vitro*, as described on page 56, lines 1-10.

Claims 2, 30, and 33 are further amended by deleting the word "substantially."

Claim 18 is amended to be directed to the improved method of claim 17, wherein the anti-gp39 antibodies that are administered are chimeric antibodies having light and heavy chain variable regions of an antibody of an Old World monkey, and constant regions of human antibodies, support for which is found, for example, at page 9, lines 15-18.

Claims 22 and 28 are amended by deleting erroneous references to "Kabat" positions. As discussed above with respect to amendment of the discussion of the P and E modifications on page 33 of the specification, it would be clear to one of skill in the art at the time of filing that the disclosed positions of the P and E modifications refer to actual amino acid positions in the antibody heavy chain, and not to "Kabat" positions. The amendment therefore does not add new matter.

Patentability Remarks:

35 U.S.C. §103(a)

Claims 2, 3, 5, 16-28, 30, and 33-39 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable in view of Black et al. (U.S. Patent No. 6,001,358), considered in combination with Schrader et al. (U.S. Patent No. 5,627,052), Burkly et al. (US2002/0028202 A1), and Wilson et al. (U.S. Patent No. 6,372,208 B1), "essentially for the reasons of record."

The applicants respectfully traverse the rejection of the claims under 35 U.S.C. § 103(a) as allegedly being obvious in view of Black et al., Schrader et al., Burkly et al., and Wilson et al. The currently amended claims of the present application are directed to the disclosed improved method of treating an autoimmune disease or disorder that expressly includes the steps of:

(1) obtaining anti-human gp39 antibodies;

(2) assaying to identify anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40;

(3) assaying to identify anti-human gp39 antibodies that compete for binding to human gp39 with murine antibody 24-31, produced by hybridoma cells assigned ATCC accession no. HB-11712;

(4) assaying *in vitro* to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells selected from the group consisting of T-cell proliferation and the production of a cytokine selected from the group consisting of IFN-γ, IL-4, and IL-2;

(5) identifying anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, compete with murine antibody 24-31 for binding to human gp39, and are non-agonistic of said human T-cell activation response; and

(6) administering a therapeutically effective amount of said anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, compete with murine antibody 24-31 for binding to human gp39, and are non-agonistic of said human T-cell activation response.

The examiner describes Black et al., the primary reference, as disclosing anti-human gp39 antibodies that compete for binding to human gp39 with murine antibody 24-31, and therapeutic methods in which such anti-gp39 antibodies are administered to treat multiple sclerosis and other diseases. The examiner further describes Black et al. as teaching that $gp39^+$ T cells produce IL-2, IL-4, and IFN-γ and that anti-gp39 antibodies can block signals delivered to T cells via gp39. The examiner acknowledges Black et al. does not describe screening to identify anti-gp-39 antibodies that affect the ability of T cells to produce cytokines such as IL-2, IL-4, and IFN-γ, or that affect the ability of T cells to proliferate. In fact, it is unclear from Black et al. whether the binding of anti-gp39 antibodies to $gp39^+$ T cells would have any effect at all on the ability of the T cells to proliferate or produce IL-2, IL-4, and IFN-γ. Moreover, Example 4 of Black et al. shows that anti-gp-39 antibodies do not inhibit *in vivo* antigen-specific proliferative responses of human T cells in the spleens of hu-PBL-scid mice, which suggests that anti-human gp-39 antibodies do not interfere with human T cell activation responses.

The secondary reference Schrader et al. is described by the examiner as teaching "methods of producing antibodies of a desired function to a variety of antigens, including IL-2 and γ-interferon," and the secondary reference Burkly et al. is described as teaching

"methods of assaying or screening the ability of antagonists such as antibodies to block a response to a particular cytokine." The secondary reference Wilson et al. is described as teaching "that CD40L-CD40 interactions are desirable given its broad activity in both T helper cell activation and function as well as the absence of redundancy in its signaling pathway." Wilson et al. also describes an assay for detecting the ability of an anti-gp39 antibody to inhibit antigen-stimulation of T cells *in vivo* comprising co-administering the anti-gp39 antibody and a T-cell-stimulating antigen to a mouse, isolating T cells from the treated mouse, and measuring the ability of the isolated T cells to proliferate *in vitro*. Wilson et al. show that T-cells isolated from a mouse that has been injected with a T-cell-stimulating antigen are able to proliferate *in vitro*, whereas co-injection of a mouse with both a T-cell-stimulating antigen and the anti-murine gp39 antibody MR1 prevents the isolated T-cells from proliferating. *See* col. 21.

The examiner alleges that one of ordinary skill in the art at the time the invention was made would have been motivated to "apply the teachings of the [secondary references] to screen and obtain antagonistic anti-gp39 antibodies with the ability to inhibit cytokines produced by activated T cells, including the inhibition of IL-2, IL-4, and γ-interferon, which were known to be products of the T-cells targeted by antagonistic anti-gp39 antibodies." The examiner further alleges that, "[a]ccording to Black et al., a person of ordinary skill in the art would have been motivated to produce this resultant ability of anti-gp39 antibodies to inhibit cytokine activity by activated T cells in order to test and select for those anti-gp39 antibodies that had the described properties of inhibiting gp39:CD40 interaction and the resultant ability of such antibodies to inhibit T cell mediated activation of immune responses in the treatment of ... multiple sclerosis." The examiner concludes that "[f]rom the teaching of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention," and that "[t]herefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary."

To establish a *prima facie* case of obviousness, the examiner must show that the prior art references themselves or the knowledge generally available to one of ordinary skill in the art would (1) provide some suggestion or motivation to modify or combine reference teachings to obtain the claimed invention, (2) teach or suggest all of the claim limitations, and

(3) provide a reasonable expectation that the claimed invention can be made or used successfully. *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). *See* M.P.E.P. § 2142.

In determining if there is obviousness in the first instance, "it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re* Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). *See* M.P.E.P. § 2142.

The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. *In re* Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness does not require absolute predictability, however, at least some degree of predictability is required. *In re* Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Combining prior art references without evidence of a suggestion, teaching, or motivation "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight." *See* Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1371-72; 56 U.S.P.Q.2d 1065 (C.A.Fed. - Cal., 2000).

The applicants submit that the combination of Black et al. with Schrader et al., Burkly et al., and Wilson et al., would not have provided suggestion, teaching, or motivation to practice the claimed invention with a reasonable expectation of success, and that the rejection of the claims under 35 U.S.C. § 103(a) as allegedly being obvious in view of Black et al., in combination with the secondary references, can only be based on hindsight in view of the teachings of the present application, and is improper.

The claimed method includes the steps of assaying *in vitro* to identify anti-human gp39 antibodies that are non-agonistic of an activation response by purified human $CD4^+$ T-cells selected from the group consisting of T-cell proliferation and the production of IL-2, IL-4, and IFN-γ, and identifying anti-human gp39 antibodies that inhibit the interaction of human gp39 with CD40, compete with murine antibody 24-31 for binding to human gp39, and are non-agonistic of said human T-cell activation response.

As noted above, Black et al. teaches that $gp39^+$ T cells produce IL-2, IL-4, and IFN-γ; however, neither Black et al. nor the secondary references provide guidance to one of ordinary skill in the art as to whether anti-human gp39 antibodies would have any effect *in vitro*, either inhibitory or stimulatory, on the production of IL-2, IL-4, or IFN-γ by purified human $CD4^+$ T-cells, or on the proliferation of purified human $CD4^+$ T-cells. **Prior to the invention of the claimed method, it was not known or suspected that anti-human gp39 antibodies could be obtained that compete for binding to human gp39 with murine antibody 24-31, inhibit the interaction of human gp39 with CD40, and are non-agonistic *in vitro* of activation responses of proliferation and production of IL-2, IL-4, and IFN-γ by purified human $CD4^+$ T cells.**

As noted above, Wilson et al. showed that an anti-murine gp39 antibody can inhibit antigen-stimulated proliferation by murine T-cells *in vivo*, whereas Black et al. taught that an anti-human gp-39 antibody does not inhibit human T cell proliferation *in vivo*. These results indicate that the effects of anti-gp39 antibodies on T cell activation responses *in vivo* are unpredictable. However, one of ordinary skill in the art would not have known whether the differences in these responses reflect differences in the signaling pathways or intercellular regulatory mechanisms that control proliferation of human and murine T cells, differences in the gp39 epitopes targeted by the antibodies, differences between the *in vivo* assay systems used by the two research groups, or other unidentified factors. In addition, one of ordinary skill in the art would not reasonably have considered responses of T cells *in vivo* to be predictive of responses of purified T cells contacted with anti-gp-39 antibodies *in vitro*. To the extent that the cited references provided motivation to assay the effects of anti-gp-39 antibodies on T cell activation responses, the teaching by Wilson et al. that T cell activation is mediated by interactions between T cells and B cells would have motivated one of ordinary skill in the art to use a multicellular assay system that includes B cells, such as the *in vivo*

assay methods described by Wilson et al. and Black et al., rather than the *in vitro* assay using purified human $CD4^+$ T-cells of the claimed invention.

As discussed in the previous response, evidence of the non-obviousness of the claimed invention is provided by Blotta et al. (1996, J. Immunol., 156:3133-3140) and Blair et al. (Feb. 2000, J. Exp. Med., 191(4):651-660), both of which taught that anti-human gp39 antibodies stimulate human $CD4^+$ T cells *in vitro* to proliferate and produce significant amounts of certain cytokines, including IFN-γ, with the amount of stimulation of T cell proliferation being dependent on the specific anti-gp39 antibody that is used. The demonstration by the present application that one can use an *in vitro* assay to screen anti-gp39 antibodies that compete with murine antibody 24-31 for binding to human gp39 and successfully identify anti-human gp39 antibodies that are non-agonistic of the proliferation of purified human $CD4^+$ T-cells and of the production of IL-2, IL-4, and IFN-γ by purified human $CD4^+$ T-cells is clear evidence that it is impossible to predict the effect of a given anti-human gp39 antibody on an activation response by purified human $CD4^+$ T cells *in vitro*. The inability to predict the effect of a given anti-human gp39 antibody will have on an activation response of purified human $CD4^+$ T cells *in vitro* is further evidenced by the demonstration in present application that the anti-human gp39 antibody TRAP-1 stimulates purified human $CD4^+$ T cells *in vitro* to proliferate and produce significant amounts of IFN-γ as well as IL-2 and IL-4.

In view of the foregoing, the applicants submit that the cited prior art references would not have provided one of ordinary skill in the art at the time the invention was made with a suggestion or motivation to perform the claimed method comprising assaying to identify anti-human gp39 antibodies inhibit the interaction of human gp39 with CD40, compete with murine antibody 24-31 for binding to human gp39, and are non-agonistic *in vitro* of an activation response by purified human $CD4^+$ T-cells selected from the group consisting of T-cell proliferation and the production of IL-2, the production of IL-4, and the production of IFN-γ. Nor could the cited references have provided a reasonable expectation of success. Withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as allegedly having been obvious in view of Black et al., Schrader et al., Burkly et al., and Wilson et al., is therefore respectfully requested.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

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